Citation:

Wei EK, Giovannucci E, Wu K, Rosner B, Fuchs CS, Willett WC, Colditz GA. Comparison of risk factors for colon and rectal cancer. Int J Cancer. 2004 Jan 20;108(3):433-42

PubMed ID: 14648711

Study Design:

prospective cohorts (pooled)

Class:

B - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To examine established risk factors to determine whether they were differentially associated with colon and rectal cancer.

Inclusion Criteria:

- None specified

Exclusion Criteria:

- participants who reported
  - previous cancer (except for nonmelanoma skin cancer)
  - ulcerative colitis
  - Crohn's disease
  - familial polyposis syndrome
  - individuals who reported implausible caloric intakes (< 800 or > 4,200 kcal for men; < 600 or > 3,500 kcal for women)
  - individuals who had a significant number of items left blank on the food frequency questionnaire (FFQ)

Description of Study Protocol:

Recruitment:

- Data from 2 prospective cohort studies:
  - Nurses' Health Study (NHS) (began in 1976) and
  - Health Professionals Follow-Up Study (HPFS) (began in 1986).

Design: pooled analysis of two cohorts

Blinding used (if applicable): N/A

Intervention (if applicable): N/A

Statistical Analysis

- for age-adjusted and multi-variate pooled logistic models, variables were modeled as dichotomous or in categories with the same cutpoints for males and females (based in literature)
    - cut-point was gender-specific only for height
- person-time contributed by each participant:
    - NHS: date of return of 1980 FFQ to date of a colon or rectal cancer diagnosis, death from any cause to May 31, 2000, whichever came first
    - HPFS: date of return of 1986 FFQ to date of a colon or rectal cancer diagnosis, death from any cause to January 31, 2000, whichever came first
- relative risks (RR): calculated by dividing the incidence rate in each category by the rate among those in the lowest category (reference category
- stratified analysis: Mantel-Haenszel summary estimator
- test for trend: medians from each category modeled as continuous variables
- adjustment for more than one variable at a time: logistic regression pooled over each 2 year time period
- test for differences in associations with colon and rectal cancer: polytomous logistic regression on the combined cohort
    - to reduce computation complexity and simplify interpretation:
        - age modeled as continuous variable
        - family history and endoscopy modeled as dichotomous variables
        - BMI, physical activity, smoking, beef as a main dish, processed meat, height, calcium, folate, alcohol and fiber: medians of the categories (quintiles) used as continuous variables

Data Collection Summary:

Timing of Measurements

- NHS:
    - began in 1976
    - questionnaires to ascertain lifestyle habits and disease history: every 2 years
    - assessment of dietary intake (FFQ):
        - 1980, 1984, 1986, and every 4 years thereafter
- HPFS:
    - began in 1986
    - questionnaires to ascertain lifestyle habits and disease history: every 2 years
    - assessment of dietary intake:
        - every four years

Dependent Variables

- colon or rectal cancer: reported on questionnaires and verified by review of hospital records and pathology reports

Independent Variables

- family history: positive iffirst-degree relatives had ever been diagnosed with colon or rectal cancer
- smoking:
  - current, past, or never
  - one pack-year = 20 cigarettes per day for 1 year
- physical activity:
  - HPFS: metabolic equivalent (MET) hours per week = time spent on each activity x typical energy expenditure for that activity in METS; added in METS for stairs and walking
  - NHS:
    - 1980 questionnaire: 5 categories of activity, each assigned a MET score for the primary activity reported
    - 1986: METs calculated
- anthropometric variables:
  - height: self-reported in baseline questionnaire
  - weight: self-reported in biennial questionnaires
  - BMI: kg/m^2
- dietary variables: FFQ
  - alcohol: baseline value
  - folate: baseline value
  - beef as a main dish: baseline value
  - processed meat: baseline value
  - calcium: cumulative value

Control Variables

- age, family history and endoscopy, BMI, physical activity, smoking, beef as a main dish, processed meat, height, calcium, folate, alcohol and fiber

Description of Actual Data Sample:

Initial N:

- NHS: N = 121,700 at baseline
- HPFS: N = 51,529 at baseline

After exclusion criteria applied:

- NHS: N = 87,733
- HPFS: N = 46,632

Age: At baseline:

- NHS: 30 to 55 years
- HPFS: 40 to 75 years

Ethnicity: not specified

Other relevant demographics:none specified

Anthropometrics

- BMI (kg/m^2):
  - Women:
    - Noncases (N = 86,857): 24.5
    - Colon cancer (N = 672): 24.7
    - Rectal cancer (N = 204): 25.4
  - Men:
    - Noncases (N = 46,030): 25.5
    - Colon cancer (N = 467): 25.8
    - Rectal cancer (N = 135): 24.9
- Height (inches):
  - Women:
    - Noncases: 64.5
    - Colon cancer: 64.9
    - Rectal cancer: 64.2
  - Men
    - Noncases: 70.1
    - Colon cancer: 70.6
    - Rectal cancer: 70.3

Location: United States

Summary of Results:

Key Findings:

- In the combined cohort (Nurses' Health Study and the Health Professionals Follow-Up Study), age, gender, family history of colon or rectal cancer, height, body mass index, physical activity, folate, intake of beef, pork or lamb as a main dish, intake of processed meat and alcohol were significantly associated with colon cancer risk.
- investigations of colon or rectal cancer should take into consideration risk factor differences by subsite.

Compared to women, men:

- were more physically active
- were taller
- had higher alcohol intake
- had slightly higher intakes of folate, calcium, and processed meats
- smoked more pack-years before age 30

Compared to colon cancer cases, rectal cancer cases tended to

- have slightly higher folate intake
- have slightly lower calcium intake
- be more physically active
- have a lower frequency of positive family history of colorectal cancer

Multivariate analysis:

- ***Variables associated with colon cancer: significant multivariate relative risks (MVRR):***

- **age**
- **sex**
  - Male: 1.00
  - Female: 0.63 (95% CI:0.54, 0.73)
- **family history**
  - NHS: 1.86 (95%CI: 1.52, 2.26)
  - HPFS: 1.69 (95%CI = 1.34, 2.14)
  - Combined cohort:: 1.81 (95% CI: 1.55, 2.10)
- **height**
  - NHS:
    - 67 to 81 inches (tallest) category =1.48 (95% CI: 1.18, .188)
    - P for trend = 0.001
  - HPFS:
    - 73 to 81 inches (tallest) category =1.50 (95% CI: 1.13, 2.00)
    - P for trend = 0.004
  - Combined cohort:
    - 71 to 72 inches = 1.24 (95% CI: 1.04, 1.46)
    - 73 to 81 inches (tallest) category = 1.50 (95% CI: 1.25, 1.79)
    - P for trend < 0.0001
- **BMI**
  - NHS:
    - >30 kg/m^2 = 1.28 (95%CI: 1.10, 1.62)
    - P for trend with increasing BMI = 0.05
  - HPFS:
    - >30 kg/m^2 = 1.85 (95% CI: 1.26, 2.72)
    - P for trend = 0.001
  - Combined cohort:
    - 25 to 29.9 kg/m^2 = 1.21 (95% CI: 1.04, 1.42),
    - > 30 kg/m^2 = 1.39 (95% CI: 1.14, 1.69)
    - P for trend = 0.001
- **physical activity**
  - NHS:
    - P for trend across 5 quintiles of MET hrs = 0.02
  - HPFS:
    - top quintile of MET hrs = 0.71 (95% CI: 0.52, 0.96)
    - P for trend = 0.04
  - Combined cohort:
    - top quintile of MET hours = 0.75 (95% CI: 0.61, 0.94)
    - P for trend = 0.001
- **folate**
  - NHS:
    - P for trend = 0.04
  - HPFS:
    - N.S.
  - Combined cohort:
    - > 400 mcg/day = 0.82(95% CI: 0.68, 0.99)
    - P for trend = 0.06
- **beef, pork, lamb as main dish**
  - NHS:
    - N.S.

- HPFS:
  - < 3 servings per month = 1.53 (95% CI: 1.01, 2.33)
- Combined cohort:
  - < 3 servings per month (lowest category of intake) = 1.43 (95% CI: 1.02, 2.02)
  - 5+ servings per week (highest category of intake) = 1.43 (95% CI: 1.00 - 2.05)

- **processed meat**
  - NHS:
    - P for trend = 0.02
  - HPFS:
    - N.S.
  - Combined cohort:
    - 5+ servings per week (highest category of intake) = 1.33 (95%CI: 1.04, 1.70)
    - P for trend = 0.008
- **alcohol**
  - NHS:
    - N.S.
  - HPFS:
    - ≥ 20 grams/day = 1.55 (95% CI: 1.05, 2.27)
    - P for trend = 0.003
  - Combined cohort:
    - ≥ 20 grams/day = 1.27 (95% CI: 1.03, 1.56)
    - P for trend = 0.003

- ***Variables associated with rectal cancer:***
  - **age**
  - **sex**
    - Male = 1.0
    - Female = 0.71 (95% CI: 0.54, 0.95)
  - suggestion of a different effect of BMI between men and women:
    - in NHS:
      - > 30 $kg/2$ = 1.85 (.126, 2.72)
      - P for trend = 0.001
    - in HPFS and combined cohort: N.S.

In polytomous logistic regression

- Family history and physical activity had significantly different risk estimates for colon versus rectal cancer
- Height had the lowest nonstatistically significant P-value for a difference between colon cancer and rectal cancer (P = 0.07)
- All other variables modeled appropriately when risk estimates were set to be the same for colon and rectal cancer

Other Findings

- Associations of smoking with colon and rectal cancer:
- NHS:
  - MVRR for colon cancer = 1.30 (1.03, 1.66) for >10 pack years, P for trend = 0.06

- HPFS
  - MVRR for rectal cancer = 1.67 (1.07, 2.62) for > 10 pack years, P for trend = 0.04

Author Conclusion:

Some risk factors, including family history, physical activity and possibly height, differ in their association with colon and rectal cancer. Because risk factors for colorectal cancer do not appear to contribute equally to colon and rectal cancers, future investigations into risk for colorectal cancer should ideally be done differentially by subsite.

Reviewer Comments:

The authors note that the number of rectal cancer cases is small, potentially obscuring possible relationships.

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions

1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	N/A

Validity Questions

1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes

2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	N/A
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	Yes
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	Yes
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	Yes
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	N/A
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A

5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	N/A
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	Yes
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	Yes

8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**		Yes
	8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
	8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
	8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
	8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
	8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
	8.6.	Was clinical significance as well as statistical significance reported?	Yes
	8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**		Yes
	9.1.	Is there a discussion of findings?	Yes
	9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**		Yes
	10.1.	Were sources of funding and investigators' affiliations described?	Yes
	10.2.	Was the study free from apparent conflict of interest?	Yes